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Research involving pediatric stem cell donors: A way forward

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Abstract

The most suitable donor for younger patients who undergo hematopoietic stem cell transplantation in the research setting is frequently a minor sibling. These cases raise the question of whether minors who serve as stem cell donors for research subjects should be regarded as research subjects themselves. Regarding pediatric donors as research subjects ensures that an IRB reviews their involvement and determines whether it is appropriate. Yet, IRBs must follow the US regulations for pediatric research, which were designed for patients and healthy volunteers, not for healthy donors. As a result, regarding pediatric donors as research subjects also can pose unnecessary obstacles to appropriate and potentially life-saving research. The present manuscript considers a new way to address this dilemma. The federal research regulations allow for waiver of some or all of the included requirements when they are unnecessary for a study or a class of studies. We argue that this option offers a way to ensure that the involvement of pediatric donors receives sufficient review and approval without inadvertently undermining valuable and potentially life-saving research.

Keywords

Transplantation; donor; pediatric; regulations

Introduction

Every year, thousands of individuals in the United States are diagnosed with life-threatening diseases for which hematopoietic stem cell (HSC) transplantation is the preferred treatment. These transplants cure many patients. They also are associated with significant morbidity and mortality, and many patients who undergo HSC transplantation are not cured. Current research aims to address these concerns.[1] For younger patients who participate in these studies, the donor who offers the best chance for a cure is frequently a minor sibling. These

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cases raise the question of whether minors who serve as stem cell donors for research subjects should themselves be considered research subjects.[2]

Regarding pediatric donors as research subjects ensures that an IRB reviews their involvement and finds it appropriate. This approach also raises an important concern. Pediatric HSC donation is permitted in the clinical setting when it offers the potential for important benefit to a close relative. In contrast, IRBs may approve pediatric research only when it offers subjects the potential for direct benefit or the risks are very low.[3,4] Regarding pediatric donors as research subjects thus has the potential to categorize as excessively risky HSC donations that are considered acceptable in the clinical setting.

The present manuscript describes a possible way to address this dilemma. US regulations allow for waiver of some or all of the included requirements when they are inappropriate for a study or class of studies.[5,6] This option, which has been used only a few times,[7] offers the possibility of developing guidelines to ensure that pediatric donors who qualify as research subjects receive appropriate protection without undermining valuable and potentially life-saving research.

When do US regulations apply to pediatric stem cell donors?

When reviewing HSC transplantation studies that involve pediatric donors, IRB's first must determine whether the donors qualify as research subjects. In the US, there are two regulatory definitions of a research subject. FDA regulations define individuals as research subjects when they receive the test article or serve as controls (21 CFR §50.3g). Department of Health and Human Services (DHHS) regulations define individuals as research subjects when an investigator obtains data through interaction with the individual, or obtains identifiable private information about the individual (45CFR §46.102).

In addition to these two regulatory definitions, it seems reasonable to regard donors as research subjects when their donating cells to a research subject exposes them to risks they would not face otherwise. To determine whether minor donors qualify as research subjects under one or more of these three definitions, consider the different types of research involving pediatric donors (Table 1).

Standard collection for a standard indication

Some studies focus on conditions for which transplantation is standard treatment. In addition, the collection procedures are the same as those used in standard clinical settings. When these studies are designed to evaluate the collection procedures, the donors qualify as research subjects under FDA and DHHS regulations. More commonly, these studies evaluate different approaches to transplantation, in which case the donors do not qualify as research subjects under FDA regulations. Because any private information that investigators collect about donors, such as their names, is not used for research purposes, these donors also do not qualify as research subjects under DHHS regulations.[8]

IRBs might assume that these donors face research risks on the grounds that standard donation procedures pose risks. However, US regulations direct IRBs to evaluate only the

risks and benefits "that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)" (46. 111 (2). While cell donation is not a therapy for donors, it seems reasonable to interpret this stipulation as suggesting that IRBs should regard as research risks only the risks donors would not face outside of research. Under the third definition, then, donors in this category do not qualify as research subjects.

Standard collection for a new indication

Some donors undergo standard collection procedures in the context of a transplant for a new indication, one that would not be transplanted in the clinical setting. These donors do not qualify as research subjects under FDA regulations (unless the research is designed to evaluate the collection procedures). Because any private information that investigators collect about the donors is not used for research purposes, they also should not be regarded as research subjects under DHHS regulations. In contrast, since these transplants would not occur absent the research, the donors face risks they would not otherwise face. This provides reason, under the third definition, to regard these donors as research subjects, even when the research is not designed to evaluate the collection procedures.

Standard collection plus

Researchers sometimes supplement standard collection procedures with additional research procedures, such as extra blood draws for research analysis. These procedures do not make the donors research subjects under the FDA regulations. In contrast, these donors qualify as research subjects under the DHHS definition since the investigators are obtaining data as the result of an intervention with the donors. This conclusion agrees with the third definition which regards the donors as research subjects because the extra procedures pose risks they would not face outside of research.

Experimental collection

Some research studies evaluate new collection methods, such as a method that might yield more cells.[9] With growing interest in cell-based therapy, investigators also might conduct research that involves obtaining cells other than stem cells. In these cases, donors qualify as research subjects under FDA regulations because they receive an intervention that is being evaluated. They also qualify as research subjects under DHHS regulations on the grounds that the investigators are interacting with the donors in order to collect generalizable knowledge. And they qualify as research subjects under the third definition because they would not otherwise face the risks of the experimental collection.

Are existing regulations appropriate for research with minor donors?

The present analysis reveals that minor donors who undergo a standard collection for a standard indication do not qualify as research subjects, unless the research is designed to evaluate the collection procedures. However, in several other scenarios, minor donors do qualify as research subjects under US regulations. In addition, we have argued that it is reasonable to regard minor donors as subjects when the research poses risks they would not otherwise face. The conclusion that pediatric donors qualify as research subjects in several

cases raises the challenge of determining whether their research involvement can be approved under US pediatric regulations.

Minimal risk (45CFR.46.404, 21CFR.50.51)

IRBs can approve research in children when it poses 'minimal' risk, defined as risks which do not exceed the risks "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (46.102 i). Although the regulations do not specify whose daily life should serve as the baseline for making this determination, there is widespread agreement that IRBs should compare the risks of pediatric research to the risks ordinarily encountered by average, healthy children.[10]

IRBs can approve, in this category, research involving pediatric donors who undergo a standard donation plus a minimal risk procedure, such as a single blood draw, for research purposes. In this case, the risks of the collection procedure do not count as research risks and the risks of the blood draw are minimal.

With respect to standard donations for non-standard indications, and experimental donations, donors undergo a collection procedure they would not undergo outside of research. Hence, the risks of the collection procedure count as research risks. Importantly, because the risks of collection procedures typically exceed the risks ordinarily encountered by average, healthy children, the participation of pediatric donors in these cases cannot be approved as minimal risk.

Minor increase over minimal risk (45CFR.46.406, 21CFR.50.53)

Pediatric studies that pose greater than minimal risk may be approved by an IRB when the risks are no greater than a minor 'increase' over minimal, and the study satisfies several additional requirements. IRBs that categorize standard collection procedures as posing a minor increase over the risks ordinarily encountered by average, healthy children could approve the participation of minor donors in this category provided the study is likely to "yield generalizable knowledge about the child's disorder or condition."

Some commentators argue that a 'condition' refers only to medical conditions which are the focus of the research in question.[11] Others regard children who are at increased risk for having an illness or disease as having a condition.[12] Because donors tend to be healthy, these approaches suggest that donors' research involvement cannot be approved in this category.

A few commentators have argued that 'condition' should be understood very broadly, allowing investigators to enroll essentially all children in this category of research.[13] One analysis supports this approach,[14] suggesting that donors have the condition of being a sibling of an individual who is a candidate for transplantation.[15] This interpretation raises the question of whether the research is likely to yield generalizable knowledge about the condition of having a sibling who is a candidate for transplantation. This might be the case for certain studies. For example, research designed to find a less invasive way of obtaining cells can obtain important knowledge for the well-being of donors. In contrast, the participation of the donor could not be approved in the category of a minor increase over

minimal risk for studies designed to develop generalizable knowledge about the condition of the recipients.

Prospect of direct benefit (45CFR.46.405, 21CFR.50.52)

US regulations allow IRBs to approve the involvement of children in research that offers a prospect of direct benefit, although the regulations do not define what constitutes a 'direct' benefit. In the clinical setting, the risks of HSC donation are justified on the grounds that it offers donors the potential psychosocial benefit of helping a close family member. On this basis, one might argue that the opportunity to help the recipient qualifies as a 'direct' benefit for donors in research.

The leading analysis defines direct benefits as potential medical benefits that result from receiving the intervention under study.[16] This definition suggests that the benefits of helping the recipient do not qualify as direct. Thus, in order to support this approach, proponents will have to develop an alternative definition that includes psychological benefits from helping a close family member.

The first challenge in this regard will be to specify who counts as a close family member. The most obvious approach would be in terms of biological criteria, such as being a first degree relative. However, if the benefits to the donor involve the psychological benefit of helping someone else, it seems that closeness should be determined based on who it is that the donor would gain psychological benefit from helping. Would the donor experience psychological benefit from helping a cousin, a step sibling or even a friend? If so, the research would qualify as prospect of direct benefit on this approach.

Second, studies find that minors gain different types of psychological benefit from participating in research. For example, one survey of adolescents found that 80.8% felt proud to be participating in research to benefit others.[17] If the psychological benefit of feeling good about helping a close family member can count as a direct benefit, it is unclear on what grounds proponents will be able to deny that the psychological benefit of feeling good about helping unrelated others does not count as a direct benefit. This raises concern that all pediatric research might ultimately be categorized as offering a prospect of direct benefit on the grounds that it offers subjects the opportunity to help others. To avoid this possibility, it seems reasonable to conclude that the involvement of pediatric donors should not be categorized as offering a prospect of direct benefit.[18]

Research otherwise not approvable by an IRB (45CFR.46.407/21CFR.50.54)

Studies that cannot be approved by an IRB may be approved through a review process which requires initial review by OHRP or FDA, a period for public comment, convening and review by a panel of experts, a recommendation by OHRP or FDA, and a final determination by the Secretary or Commissioner (Text Box l).[19] Importantly, each individual study that cannot be approved by an IRB must go through this process or be abandoned.

Relying on this extensive process makes sense for individual studies that cannot be approved by an IRB because they raise important ethical concerns. For example, this additional review makes sense for studies which involve donors undergoing additional research procedures

that pose significant risk. In contrast, this level of additional review does not seem to make sense for many other studies. For example, the present analysis suggests that many studies involving standard collection procedures for a new indication cannot be approved by an IRB. The reason is not that standard collection procedures pose greater risks in research than they pose in the clinical setting. Rather, the problem is that the research regulations were designed for patients and healthy volunteers, not for pediatric donors.

Most non-beneficial research with healthy children involves early phase studies that offer an uncertain potential to benefit future individuals who are unrelated to the subjects. Under these conditions, it makes sense to limit pediatric research to studies that pose minimal risk, or at most a minor increase over minimal risk. In contrast, HSC transplantation research offers potentially life-saving treatment to a close relative of the donor. Because of this mismatch between HSC transplantation research and the types of research for which the pediatric regulations were designed, there will be a number of studies involving pediatric donors for which existing regulations seem excessive. Is there some way to avoid requiring that each of these studies undergoes the special review process?

Waiver

While not widely recognized, the federal regulations allow for waiving some or all of the included requirements when they are unnecessary for a study or a class of studies.[5,6] This option was used previously with respect to epidemiological research involving prisoners.[20] Current US regulations limit research with prisoners that does not have a “reasonable probability of improving the health or well-being of the subject” to studies of incarceration and criminal behavior, study of prisons and prisoners, and studies of conditions that particularly affect prisoners (45cfr46.306).

These limitations offer important protection for prisoners. They also pose significant obstacles to epidemiologic studies that attempt to identify all cases of a given illness. Such studies offer important social value, and generally use interventions (e.g. interviews and buccal swabs) that pose relatively low risks. Nonetheless, these studies typically cannot be approved under US regulations because they do not focus on prisons or prisoners. Because there is a good reason to enroll prisoners in these studies, a waiver of this requirement was sought for the class of epidemiological studies related to chronic diseases, injuries, and environmental health.

This class of research is low risk, but not risk free. For example, the waiver explicitly covers studies in which “all persons with HIV, but with none of the known risk factors for HIV” are asked to answer questions and provide a blood specimen.[20] Breach of confidentiality in this type of study could place prisoners at risk of stigma or abuse. The request for a waiver was nonetheless approved, with the provision that individual studies within the covered class must be approved by an IRB. Moreover, to approve studies under the waiver, the reviewing IRB had to find that sufficient safeguards are included for prisoners.[20]

This example highlights the possibility of obtaining a waiver from one or more of the research requirements when they are unnecessary for a defined class of studies. Can this

approach be used to address the dilemma posed by studies involving pediatric stem cell donors who qualify as research subjects?

Alternative requirements to protect pediatric donors

The present dilemma arises when two conditions are satisfied: 1. The risks donors face from collection procedures count as research risks; and 2. The risks of the collection procedures exceed the risks average, healthy children ordinarily encounter. In these cases, current regulations make it difficult to approve the participation of pediatric donors. Fortunately, these two conditions also suggest a possible solution.

Comparing the risks that healthy pediatric subjects face to the risks ordinarily encountered in daily life by average, healthy children makes sense for most pediatric research. However, this approach seems problematic for evaluating the acceptability of the risks of collection procedures that occur in the research context. One way to avoid this problem would be to compare the risks faced by donors who qualify as research subjects to the risks of collection procedures that are regarded as appropriate in the clinical setting. The assumption here is that, if a given level of risk is considered acceptable for pediatric donors in the clinical setting, that same level of risk can be acceptable in the research setting.

The proposed waiver would stipulate that individual studies within the class of studies must be reviewed and approved by an IRB that satisfies all the regulations on IRB composition and review. In addition, the IRB must find that the study satisfies all applicable regulations, including requirements on parental or guardian permission and pediatric assent. The one exception being that the IRB would compare the risks donors face to the risks that are acceptable for pediatric donors in the clinical setting. For example, on the assumption that standard collection procedures are acceptable, the IRB would compare the risks the donors face to the risks of standard collection procedures. Consider how this approach (Text Box 2) would apply to the case of a donor undergoing a standard collection for a new indication, with no added research procedures.

Since the donor would not face the risks of donation outside of the research, these risks qualify as research risks under the third definition. In addition, since the risks of a standard collection exceed the risks ordinarily encountered by healthy children, this study cannot be approved as minimal risk. We have also argued that it cannot be approved in the category of direct benefit and frequently cannot be approved as a minor increase over minimal risk. Under current regulations, then, each of these studies is required to undergo special review. In contrast, under the proposed waiver, the IRB would compare the risks of the collection to the risks of an appropriate clinical collection. Assuming that standard collection procedures are appropriate for minor donors, it could be approved under the waiver.

Studies in the category of ‘standard collection plus’ also could be approved under the waiver provided the addition research procedures pose only minimal risk as defined by current regulations. For example, a standard collection for a new indication that includes a research survey and a single research blood draw could be approved under the waiver.

Experimental collections could be approved under the waiver when the risks are not greater than the risks of an appropriate clinical collection. For example, an experimental collection which is thought to pose lower risks than a standard collection could be approved. What about experimental collections that pose a minor increase over the risks of a standard collection, such as a slightly longer procedure to collect more cells?

IRBs typically can approve research that poses a minor increase over what is regarded as minimal risk. This supports allowing experimental procedures that pose a minor increase over the risks of an appropriate clinical collection. Yet, the risks faced by donors already exceed the risks typically allowed in pediatric research, suggesting that it might make sense to limit IRBs to approving studies that involve pediatric donors facing risks that do not exceed the level of risks posed by an appropriate collection procedure. Future research will be needed to settle this question.

Finally, consider how the present approach would address the debate over the use of granulocyte colony stimulating factor (G-CSF). G-CSF can increase the number of hematopoietic stem cells circulating in the peripheral blood.[9] Since G-CSF was used in many pediatric centers, one might regard its use as part of an appropriate clinical collection. In that case, it could be approved under the waiver. If a minor increase over minimal risk is permitted, the use of G-CSF also could be approved under the waiver if an IRB finds that the risks are no more than a minor increase over the risks of an appropriate clinical collection. If the risks of G-CSF are deemed to be more than a minor increase over the risks of an appropriate clinical collection, it could not be approved under the waiver and would need to obtain special review and approval.

Conclusion

Pediatric research regulations were intended for patients and healthy volunteers. As a result, they have the potential to undermine appropriate and potentially life-saving studies involving pediatric stem cell donors. The present manuscript argues that a possible way to address this dilemma would be to seek a waiver of the current definition of minimal risk for the class of studies involving pediatric donors who qualify as research subjects. In place of the existing regulatory definition, IRBs would assess whether the risks to the donor exceed (a minor increase over) the risks of an appropriate clinical collection, such as a standard collection procedure.

To implement this approach, it will be necessary to convene a group of experts to evaluate this proposal, to make any changes deemed appropriate, and to submit a proposal for a waiver for the defined class of studies to the relevant federal agencies. This group should consider whether the risk limit should be minimal risk or minor increase over minimal risk. It also should provide guidelines on determining which collection procedures are appropriate in the clinical setting. This approach provides an opportunity to ensure that research with pediatric donors who qualify as research subjects undergoes independent review to ensure that their involvement is appropriate. It also ensures donors do not face excessive risks, despite the waiver of the regulatory definition of minimal risk.

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Text Box 1

OHRP* 407 review process

1. Agency review to determine whether conditions for 407 review have been met
2. Establishment of a panel of experts
3. Request for public comments published in the Federal Register for 60 days
4. Expert panel reviews the protocol
5. Initial recommendations from the individual panel members
6. Posting of the panel members' recommendations
7. Continuation of the public comment period for at least 30 days
8. Agency recommendation within 90 days of the convened panel meeting
9. Final determination by the Departmental secretary
10. Final decision transmitted to stakeholders

* While the FDA special review process is similar, it differs in a few ways

Text Box 2

Proposed requirements for waiver

1. The study offers the recipient a potential for clinical benefit that is similar to, or greater than the potential benefit offered by available options, if any, outside of the research context,
2. The relationship between the donor and the recipient is such that it is appropriate to ask the donor to face the risks of donation to benefit the recipient,
3. The risks of the donation procedure do not exceed (a minor increase over) the risks of an appropriate clinical donation for children of a similar age,
4. An IRB find that the study satisfies all other applicable regulations, including the requirements on parental or guardian permission and pediatric assent, and
5. Any added research procedures that donors undergo pose no greater than minimal risk as defined by US federal regulations.

Table 1
Four categories of research involving pediatric donors

Study Type	Donor a subject?	Approval by IRB under current regulations?	Approvable under Waiver?
Standard collection, Standard indication	No [+]	N/A	N/A
Standard collection, New indication	Yes	No	Yes
Standard collection plus	Yes	Yes, if the added procedures are minimal risk; no for new indication	Yes, if the added procedures are minimal risk (or minor increase over minimal risk) [*]
Experimental collection	Yes	No	Yes, if risks not greater than an appropriate clinical collection (or minor increase over minimal risk) [*]

[+] Unless the research is designed to evaluate standard collection procedures

[*] Current proposal leaves for future research the question of whether to allow a minor increase over the risks of an appropriate clinical collection